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Intercolonial Medical Congress of Australasia,

THIRD SESSION, SYDNEY, 1892.

Section of Anatomy, Physiology, Pathology and Pharmacology.

PRESIDENT'S ADDRESS

BY

H. B. ALLEN, M.D.

Reprinted from the "Australian Medical Journal," November 15, 1892.

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By H. B. Allen, M.D. Melb.

President of the Medical Society of Victoria, Professor of Anatomy and Pathology in the University of Melbourne, and Pathologist to the Melbourne Hospital.

In opening the proceedings of this Section, I must in the first place express my appreciation of the great honour implied in the invitation to become your President. In view of the enormous scope of the Section, I should have felt much trepidation concerning the responsibilities that devolve upon me, were it not for the presence of a distinguished band of Vice-Presidents and Secretaries, worthily representing every department.

Anatomy, Physiology, Pathology, Therapeutics,—Being, Doing, Suffering, Healing,—all life is before us, all the knowledge of the body in health and in disease that underlies the work of the physician or surgeon. Nor can we separate these four great divisions of medical science from their foundations in Chemistry, Biology and Physics, now happily made a compulsory part of the curriculum of all medical students throughout the United Kingdom. From the beginning of 1892, the first year of medical study must, according to the decision of the General Council of Medical Education and Registration, be devoted to these three subjects. The Universities of Australasia can congratulate themselves on having from the outset recognised the necessity for such preliminary training, and find themselves already in line with the new departure. The advocates of reform in the General Council pointed to the practice of our Universities to prove that such scientific education could without hardship be made compulsory.

Anatomy, Physiology, Pathology, Therapeutics,—each is living, advancing, becoming more complex and at the same time more simple. As we slowly grasp the essential principles, order is evolved amidst the chaos of accumulating details. Human anatomy is by many considered a branch of science almost perfected, in the further progress of which none but specialists have an interest. To show that this is far from being true, I need only point to the great changes that are being made in

the principal text-books. "Quain's Anatomy," the successive editions of which embody the history of anatomy in modern times, is again being re-modelled under the learned and laborious care of Professors Schäfer and Thane. All honour and thanks to them for the parts of their work already published. In the department of Applied Anatomy, Edmund Owen's "Manual for Senior Students," fills a large lacuna. In what may be termed the philosophy of Anatomy, the appearance of Professor Andrew Macalister's text-book has produced a marked effect on the studies of candidates for the higher qualifications of the Examining Boards. Extensive use is now made of our rapidly advancing knowledge of embryology, both human and comparative, and of the morphology of lower animals. These methods of enquiry are by no means new, but they have undergone almost a *renaissance* by the greater range and intensity of their employment. Long ago the veterans of research watched with wonder the development of the circulation, and their labours explained the anomalies so commonly seen in the heart and in the great vessels. The same methods are now zealously applied in every part of the body. Light has thus been brought into many a dark place. For example, in the hand and foot we can trace the evolution of the special muscles, from their first simple symmetrical arrangement around the bones of each finger or toe, step by step up to their disposition in the adult man, where symmetry has been subordinated to specialisation of function. In this developmental process lies the explanation of most of the irregularities that from time to time present themselves. The study of the condition of the limbs of the fœtus during the various periods of gestation has done much to simplify our ideas concerning congenital club-foot.

To take another example, the central part of the thyroid gland is known to be the retrograding remnant of an organ provided with a duct which opened at the foramen cæcum on the dorsum of the tongue, while the lateral parts of the gland were developed in connection with the fourth branchial pouch. Both the central and the lateral portions were at first tubular buds from the pharynx, ending in racemose alveoli. In man, the duct usually withers away, but not always. From time to time a persistent thyro-glossal duct is found, and even in its absence traces of its former existence may appear in the form of supernumerary glands in various

places between the thyroid body and the tongue. Originally the gland was distinctly a secreting organ, the products of its activity escaping into the pharynx; and though in man the central portion shrinks into the isthmus and the occasional pyramidal lobe, and though the general tissue of the gland is changed into a series of capsules containing an altered colloid substance, the connection of the organ with mucin formation remains manifest. For it is well known that in man, in monkeys, and generally in carnivora, removal of the thyroid is often followed by a kind of myxœdema throughout the body. According to Horsley, the myxœdema is one stage in a train of phenomena arising from a profound disturbance of the nutrition of the body, the first stage being manifested by neurotic troubles, the second by myxœdema, and the third by cretinism and emaciation. In order to prevent these evils, several surgeons when removing goitrous tumours have grafted a piece of thyroid tissue into the peritoneal or subperitoneal tissue or elsewhere. Good results have been attained in some cases, but it is difficult to secure the permanence of the engrafted tissue. Even the myxœdema of cretins has been favourably influenced by similar measures. The exact explanation of the control which the thyroid exercises over the nutrition of the body is doubtful. Gentle pressure causes the colloid substance to pass from the thyroid into the lymphatics; and microscopic sections show the existence of colloid in spaces and clefts between the vesicles, probably lymph spaces. Hence, in the opinion of Horsley and others, the thyroid continues during life to secrete some substance which is absorbed, and plays a useful function in the general metabolism of the body.

In the spinal cord we have learned not only to differentiate the anatomical elements, but also to assign them their respective functions with a precision far beyond the possibilities of former times. The grey matter of the cord is no longer spoken of in general terms. The visceral and vasomotor centres of the lateral and posterior horns and the inhibitory centre of Clarke's column have been more or less fully identified, as well as the great motor column of the anterior cornu. Much has been done in the direction of defining the motor and sensory areas in the white substance, for example to distinguish not only the paths of voluntary and vasomotor impulses, but also the tracks for sensa-

tions of touch, temperature and pain, for those related to the superficial and deep reflexes, and for those conveyed by the sacral, lumbar, dorsal and brachial nerves. How greatly the study of the structure of the brain has been simplified by the assistance of embryology. Many of the old difficulties have disappeared, such as the relation of the lateral ventricles to the third ventricle and the development of their cornua; the connexion of the corpus striatum with the central convolutions; the history of the olfactory nerve, and its course through the uncinate convolution and the fornix into the subthalamic region; the relation of the pineal gland to the central pineal eye, which my colleague, Professor Spencer, demonstrated so excellently in the lacertilia; the probable origin of the peduncles of the gland from an old optic centre in the front of the thalamus; the possible development of the pituitary body in connexion with an obsolete sense organ, and of the locus niger of the crus cerebri, that curious detached mass of nerve cells, with an archaic mouth. There is no need to remind you in any detail of the many sources from which our new knowledge has come. Minute anatomy, embryology and experimental physiology have each and all made vast contributions; and, as in many other departments, the crowning work is derived from the clinical and pathological sides. Gradually we are attaining the power to localise lesions of the nervous centres with comparative accuracy, and to explain the complicated symptoms produced by them. The surgery of the brain has given rise to a large literature. Already it has been possible to collect in a useful volume the practical results obtained in the surgery of the spinal cord. But, now and ever, as Dr. John Williams insisted during the First Session of this Congress, we need a thorough co-operation between the clinical and the pathological workers. Pathological observations of the greatest interest are robbed of most of their value when an adequate clinical history is not available; and the most complete and accurate clinical histories are of comparatively little worth, unless the pathological record is equally full and reliable. But the field of labour is vast, while the workers are few. I rejoice to see signs that a better time is coming, that numbers of distinguished young graduates will come to the rescue and make possible the minute examinations, the precise records, that are so greatly needed.

In the special domain of Pathology, how phenomenal has been the advance of knowledge, since Sir James Paget's masterly lectures, commencing in 1847, taught English surgeons the essential doctrines of inflammation and repair. Here also the new development has been largely dependent on the aid afforded by general biology. Two instances at once suggest themselves. The well known lectures of Bland Sutton were based on the systematic examination of the bodies of twelve thousand animals, pertaining to the most varied branches of the vertebrate sub-kingdom. Most of this material was afforded by animals dying in the gardens of the Zoological Society; but this special field of research, which Sutton so well appreciated, did not keep him away from other theatres of pathological work. Years of patient observation in the post-mortem room and museum of Middlesex Hospital, and careful dissection of over eight hundred fœtuses, aided to give him a sound and comprehensive grip of comparative pathology, and enabled him to produce his delightful and stimulating volume.

Together with these studies of morbid processes in vertebrates, we may select for special mention the brilliant lectures of Metchnikoff on the comparative anatomy of inflammation, delivered at the *Institut Pasteur* in April and May, 1891. He lamented that pathologists had neglected too much the comparative method, though engaged with problems of the most complex character, in which no final results could well be expected unless the various phenomena were disentangled and studied separately. Hence he watched the process of inflammation in the amphioxus and in the tadpole's tail, so that the disturbances of the circulation should be of the simplest kind known among vertebrates; he set himself to learn if inflammation could be produced in animals destitute of vessels, and if so, what was the behaviour of the nervous system. He carried his researches into the domain of animals composed of masses of undifferentiated cells, and even into that of the unicellular organisms. He inquired whether the vegetable kingdom could show any phenomena comparable with those of inflammation. In this way he was enabled to describe and figure the effects of injury and of invasion by micro-organisms in various living forms, such as amœbæ, infusoria and sponges, and so on through the series of invertebrates till he reached

the simpler forms of the vertebrate sub-kingdom. He brought under review the digestive action of monads, the chemotaxis or chemical attractions and repulsions of the plasmodia of myxomycetes, the phagocytic phenomena of sponges and of various higher forms of life. According to Metchnikoff, the primitive essence of inflammation is a digestive action of protoplasm directed against noxious agents. This defensive power belongs to the whole or almost the whole organism of protozoa, and to the whole plasmodic mass of myxomycetes, but from the sponges upwards it concentrates itself in the mesoderm. The phagocytic cells of this layer approach, envelope, and destroy the noxious agents. The reaction is slow in the simpler forms of life, since the defending cells can approach the noxious agent only by their own amœboid movements; but it becomes much more rapid with the appearance of blood-vessels and blood corpuscles. By the aid of the blood-stream the organism can at any moment hurry a great number of phagocytes to the endangered spot. From these laborious researches, Metchnikoff concludes that "the essential and primordial factor of a typical inflammation consists in a reaction of the phagocytes against the injurious agent." In the course of his lectures, he lays stress upon the general leucocytosis, or accumulation of pale corpuscles in the blood, that is seen in erysipelas, croupous pneumonia, anthrax, and other bacterial diseases. In pneumonia, the leucocytosis accurately follows the march of the fever, and ends suddenly or gradually with the crisis or lysis of the disease. The same phenomenon may be induced by injecting into the blood the soluble products of micro-organisms, such as the bacillus pyocyaneus; but it is not seen in all bacterial fevers, being absent in typhoid. The ordinary phenomena of inflammation have, according to Metchnikoff, one definite purpose, to cause a great afflux of phagocytes towards the injured part. He connects the local dilatation of the vessels with the vasomotor system, and points out that Cohnheim, in endeavouring to exclude the action of the nerves, neglected those that accompany the vessels. The salutary influence of the nervous system over the process of inflammation is illustrated by Samuel's experiment. In a rabbit, congestion of one ear is caused by section of the trunk of the sympathetic, while inhibition of the sympathetic in the other ear is prevented by section of the

sensory nerves. Both ears are now treated with water at 54° C. The first ear undergoes inflammation, with speedy cure; while the second shows no hyperæmia, but passes through stasis into gangrene. Having thus dealt with the increase of the leucocytes in the blood, and with the dilatation of the vessels in the injured part, Metchnikoff explains the doctrine of chemotaxis, the attraction of phagocytes to the point of danger, or their repulsion from it. Leber showed that a crystallisable substance extracted from cultures of the staphylococcus aureus exercises an attractive influence over leucocytes, so that if a tube containing this material is inserted into the anterior chamber of the eye, the pale corpuscles crowd into the tube against the action of gravity. Various observers have shown that this influence is manifested by most microbes, that living organisms produce a greater effect than dead ones, and that leucin also possesses this attractive power. On the other hand, a few very virulent microbes, such as those of chicken cholera, and also various reagents such as lactic acid, alcohol, or quinine, repel the advance of leucocytes. Other substances again are indifferent. Thus we are introduced to positive and negative chemotaxis, the attractive or repulsive influence which microbes and their products exercise over leucocytes. Migration is, for Metchnikoff, essentially an active process. The pale corpuscles fall out of the central current in the veins mainly for mechanical reasons, but their passage through the walls of the vessels is due to their own amœboid movements, though facilitated by changes in the vascular lining. Such migration will not occur without a positive chemotaxis, a sensibility of the leucocytes to some attraction in the tissues. This sensibility plays an altogether preponderant part in inflammatory disorders. If it is in a positive state, the leucocytes emigrate in spite of feeble dilatation of the vessels; but if it is negative, no migration will occur, although the vessels are dilated. If some tubercular bacilli are inserted under the skin of a guinea-pig's ear, there is only slight dilatation of the vessels with abundant diapedesis; while if a few septicæmic vibrios are introduced instead, there is considerable dilatation, but almost no diapedesis. When the same microbe is used, similar differences are found to exist between protected and unprotected animals. Thus, if some vibrios are inoculated under the skin of the ear of vaccinated and unvaccinated guinea-pigs, the resulting inflamma-

tion is much greater in the unprotected animals; the vascular dilatation, the local heat, and the serous exudation are comparatively excessive, but the migration of leucocytes is much less abundant. In other words, the protective vaccination encourages the phagocytic reaction, while limiting the other phenomena of inflammation. If the sensibility of leucocytes is annulled by chloroform or paraldehyde, without paralysing their amœboid movements, diapedesis is effectually prevented. When the leucocytes have travelled into the tissues, they approach, surround, digest and destroy the invading microbes. But the various kinds of leucocytes differ greatly in their powers. The little lymphocytes, and those which stain so deeply with eosin, have no phagocytic power; the larger mononuclear leucocytes devour the bacilli of leprosy, but do not assail either the streptococci of erysipelas or the gonococci, both of which are attacked by the more numerous polynuclear emigrants. Soluble ferments have been found in leucocytes, with power to convert starch, fibrin and gelatine, the digestion being of a neutral or alkaline type. The activity of these ferments is destroyed by heat. Thus Metchnikoff includes in his doctrine of phagocytism the multiplication of leucocytes in the blood, the afflux of blood containing leucocytes to the invaded tissue, the sensibility of the leucocytes in the vessels to substances diffusing from the area of bacterial infection, their active migration into the tissues, and their direct action upon the microbes. Stress is also laid on an active state of the endothelium of the vessels, favouring exudation and emigration, the endothelial cells also displaying marked phagocytic power. The mobile cells of connective tissue, for instance in the tadpole's tail, also act as phagocytes, but their number is so limited that their action is relatively unimportant. Metchnikoff formerly taught that the fixed corpuscles of connective tissue were also endowed with phagocytic power, but further researches have led him to a contrary conclusion. Finally he concludes that, in the progressive series of living forms, there is a gradual evolution of the phagocytic re-action. Among the daphniæ, it fails altogether in many diseases. It is more powerful in amphibia, and still more in rabbits. Yet, in the small animals of the laboratory, we meet with many overwhelming diseases in

which the reaction of the leucocytes is absent, being prevented by the poisonous products of the microbes. In man and in the higher animals generally, such diseases are infinitely less frequent.

Metchnikoff's views have been confirmed in every essential point by Ruffer's researches concerning quarter-evil. The leucocytes gathered to the spot where the microbes had been introduced, being attracted by the chemical poisons secreted by the bacilli. They directly attacked the invading microbes, taking them into their own substance and destroying them. The cellular migration at the point of inoculation varied inversely with the strength and quantity of the virus introduced, but was directly proportionate to the duration and curability of the disease. If by any cause, either mechanical or chemical, the leucocytes were prevented from reaching the virus, the disease invariably progressed and the animal died. For instance, the introduction of lactic acid prevented diapedesis, and gave a free course to the invaders. The case was altogether different as regards fluid exudation. It would rather appear as if diapedesis and exudation stood in some inverse relation to each other. In malignant cases with rapid death, there was abundant thin sero-sanguineous exudation, but this had no power to arrest the disease; on the contrary, the bacilli grew rapidly in it, and acquired a greatly increased virulence. In spite of the abundant outpouring of serum, there is not a sign that the microbes are injuriously affected by it. In animals which resist the invasion, a tenacious solid material accumulates around the implanted virus, thus presenting a marked contrast with the phenomena of malignantly progressive cases. Other interesting arguments, based largely on pneumonia, were adduced by Adami in the recent discussion on phagocytosis before the Pathological Society of London.

The doctrine of phagocytosis has not met with general acceptance. Klein has gone so far as to declare that, as regards the destruction of bacteria, the leucocytes might as well be absent. Burdon Sanderson, in his comprehensive Croonian lectures, maintains that all pathogenous microbes show signs of structural degeneration if they remain a sufficient time in relation with living protoplasm. The degeneration occurs in blood, in lymph, and in tissue. When leucocytes are present, the microbes that remain free show the same changes as those which are incor-

porated by the leucocytes, and in the same degree. In general, vigorous microbes are not incorporated, so that incorporation is a sign of impaired vitality and diminished resistance. Non-corpuscular liquids, such as aqueous humour, pericardial fluid, serum of blood, or lymph from beneath the skin of a frog, all possess a toxic power over bacteria. In erysipelas, it is difficult to imagine that the invading myriads of streptococci can be effectually opposed by the leucocytes which follow in their train. Leucocytes do not appear at the place or time that they are wanted. In cases where Metchnikoff saw only an arrest of diapedesis, Sanderson sees an inhibition of the whole process of inflammation. Frequently after inoculation, suppuration occurs in animals naturally or artificially immune, while infection occurs in others. The destructive action of the body against microbes resides both in the blood and in the tissues, in organised protoplasm and in intercellular fluid. The contest which takes place in the organism is not a hand-to-hand fight between the microbes and the living elements of the invaded territory, but one in which both act at a distance. The weapons on both sides are poisons and counter-poisons, toxines and anti-toxines. Thus the question of infection becomes more and more chemical, *less* morphological. "We care for microphytes not as botanical species, but as makers of toxines, and for toxines not as chemical compounds, but as producers of disease."

Though the difference of opinion is so great, Sanderson admits with reservation the facts submitted by Metchnikoff. Microbes, though alive and virulent, are in laboratory experiments incorporated and destroyed by leucocytes. Metchnikoff is thoroughly aware that in other experiments microbes have been destroyed by the action of non-corpuscular fluids. Each recognises a limited foundation of truth in the other's position, but each maintains that the foundation on which the other builds is so limited as not to affect the main question.

Metchnikoff devotes a special chapter to serous inflammations, which he classifies and studies in detail, in order to test whether in actual life the serum of blood can destroy bacteria. The serum of rats kills the bacilli of anthrax, and that of guinea-pigs is toxic to the septicæmic vibrio, but the power so manifest *in vitro* is not exercised in the living animal. Almost without exception it is

found that though the serum of an animal kills certain bacilli, these very bacilli can grow and flourish in the living body of that animal. The serum of rabbits vaccinated against tetanus destroys large quantities of the tetanic toxine, but in tetanus serous inflammation is conspicuously absent. After studying a number of diseases, Metchnikoff concludes that serous inflammation is not a salutary reaction with the object of converting toxine into anti-toxine. Possibly the serous exudation serves to dilute the toxines and render them less active. From the standpoint of comparative pathology, serous inflammation is of much more recent date than the reaction of leucocytes. There is no trace of it among inverte-brates, whether provided with a circulation or not. It is rarely seen, even in the least degree, among amphibia. From every point of view, serous inflammation is much less important than that which is accompanied by accumulation of phagocytes in the focus of inflammation.

The action of rat serum upon the bacillus of anthrax has recently been studied further by Metchnikoff and Roux. If a capillary tube, open at one end and containing rat serum, is placed under the skin of a mouse, leucocytes rapidly swarm into the tube. The serum attracts the leucocytes, or in other words exer-cises a positive chemotaxis. If the serum of a rat and a culture of anthrax bacilli are introduced together, the serum acts directly upon bacilli, just as in laboratory experiments, and it also attracts the leucocytes. The bacilli then perish, being ingested and destroyed by the leucocytes. But the protective action of the serum is purely local. If the serum and the bacilli are introduced in different places, the bacilli flourish and the animal dies of anthrax.

It is not surprising that such a contest of opinions should arise. The study of micro-organisms is beset with difficulties. In the domain of morphology, how easily mistakes may occur. Thus in several histological preparations made by my demonstrator, Mr. Cherry, a ray fungus was present, closely resembling actinomyces; careful examination showed that it was on, and not in, the sections. On further enquiry, a similar organism was found in the sediment of a pressure filter in the laboratory, connected with the Melbourne water supply. So also when Dr. Katz was examining the same water supply under the direction of the Royal Sanitary Com-mission in 1889, he found several microphytes resembling the

bacillus of typhoid. One of these was mobile, grew on potato precisely like typhoid, and resembled typhoid closely in its cultures on gelatine, excepting that after the fifth day the colonies invariably caused slow liquefaction.

The morphological difficulties, however, are trifling in comparison with those which attend the chemistry of bacteria. Ptomaines and other alkaloids are relatively manageable; but what chemist will undertake to speak confidently concerning albumoses, paratoloids and enzymes? Unstable as these compounds are, sometimes defying analysis, information is rapidly accumulating concerning their actions, and before long many of them will certainly be in frequent use in the combat with infectious diseases. The microbes and their enzymes must be distinguished from the alkaloids and albumoses, which they form by digesting proteid substances. Alkaloids include ptomaines and leucomaines, but the latter are physiological products, such as xanthin and kreatinin, not formed by the action of microbes, so that they need not detain us at present. Ptomaines are the alkaloids formed by putrefactive organisms. As a rule they are colourless oily liquids, but many have been separated in crystalline form. They are strongly alkaline, neutralising the most powerful acids. Some contain carbon, hydrogen and nitrogen, but others contain oxygen also. An example of those not containing oxygen is afforded by mydaleine, the intensely poisonous alkaloid formed in dead bodies after the second or third week; and of those containing oxygen by muscarine, the powerful poison of toadstools, which is obtained also from putrefying fish. Similar alkaloids are formed by many pathogenic microbes, such as the bacilli of anthrax and of typhoid fever, and others have been isolated in cases of scarlatina and other diseases concerning the causation of which no exact information has been obtained.

Albumoses are quite distinct from alkaloids, being proteid substances chemically indistinguishable from the intermediate products formed during the digestion of albumen. They have been obtained from cultures of the bacilli of anthrax, typhoid, diphtheria, cholera, tetanus, &c., and from cultures of the staphylococcus aureus. Those of anthrax may be taken as typical examples. As Sydney Martin points out, when the bacillus anthracis is grown in a proteid medium, it digests the proteid in

the same fashion as pepsin, producing hetero-albumose, proto-albumose, deutero-albumose, and peptone. Its further action resembles that of pancreatic ferment, in splitting up the proteid matter so as to form leucin and tyrosin, but it differs from trypsin in that its final product is an alkaloid. In the living body the alkaloid is produced more abundantly than the albumoses, and is the chief agent in causing death. The coma and the local œdema are both due to the alkaloid, while the febrile phenomena are referable to the albumoses.

Of the albumoses, hetero-albumose is nearest to albumen; it resembles globulin, being coagulated by heat, insoluble in water, but soluble in weak saline solutions. Proto-albumose is soluble in water either cold or boiling, but is precipitated by saturation of the solution with sodic chloride or by nitric acid. Deutero-albumose is more closely related to peptone, not being precipitated by saturation with sodic chloride nor by nitric acid. All these albumoses differ from peptone in not dialysing freely, and in being precipitated by saturation with neutral ammonium sulphate.

The tuberculin of Koch is neither an alkaloid nor an albumose. It is neutral, resists high temperatures, and dialyses readily. It differs from peptones in several particulars, specially in being precipitated by ferric acetate. Koch calls the active principle paratoloid.

Concerning the soluble ferments or enzymes formed by microbes, much information has accumulated; but the sum of our knowledge is as nothing compared with the immensity of our ignorance. Some enzymes have powers as ferments resembling those of the microbes that produce them. Some excite in the bodies of animals toxic symptoms exactly resembling those caused by the living microbes from which they were derived. But in many cases the enzymes are so closely connected with alkaloids or albumoses, that it is difficult or impossible to speak of them separately. An interesting example of the relation of the ferment to the albumoses is afforded by diphtheria. Sydney Martin states that when the bacilli are grown in broth, to which alkali-albumen has been added instead of peptone, the alkali-albumen is converted into proto- and deutero-albumose with traces of an organic acid. These albumoses, when inoculated, cause fever, loss of weight and paralysis, with degeneration of the peripheral nerves, the muscles and

the heart, while the nervous centres remain unaffected. The organic acid produces like results, but in less degree. The same albumoses and acid are found in considerable quantity in the internal organs, notably in the spleen, of diphtheritic subjects. The membrane in the throat is in process of digestion, hetero-albumose being first produced, and subsequently proto- and deutero-albumose, with traces of the organic acid. An extract containing all the proteids of the membrane, when injected into rabbits, causes all the phenomena above mentioned; but a single small dose produces results which only multiple doses of the albumoses can effect. Moreover, the albumoses may be present in the membrane in only trivial amount when they are comparatively abundant in the spleen. For these and other reasons it is argued that the toxic effect is largely due to a ferment. According to Martin, the bacillus growing in the membrane liberates a ferment which, when absorbed, digests the proteids of the body, forming albumoses and an organic acid; these products of digestion are the lethal agents, and cause the fever, depression and paralysis.

The defensive proteids of the body must be distinguished carefully from the poisonous albumoses—the anti-toxines from the toxines. When an animal is gradually accustomed to injection of a toxine, it in many instances becomes resistant to otherwise fatal doses. A defensive proteid is formed in the body, not however from the toxine, but as a result of the metabolism of the body itself. Such proteids have been isolated, and found to consist of albuminous bodies, which, like ferments, are soluble in a 50 per cent. solution of glycerine, and are destroyed by moderate heat. Hankin proposes to classify the defensive proteids according as they exist naturally in the body, or are found only in animals artificially made resistant against some disease. He would call the former "sozins," and the latter "phylaxins." Sozins are found in all animals, and act on numerous microbes or on their products. Phylaxins appear to act only on one microbe or its products. Sozins and phylaxins are further divided according as they act on the microbe or on the toxine formed by it. Mycosozins and mycophylaxins act upon microbes, toxosozins and toxophylaxins upon the toxines formed by them. Hankin first obtained a defensive proteid (known as cell globulin B) from the spleen and lymphatic glands—from cells that were potential

phagocytes. He holds that possibly these proteids are the weapons used by the phagocytes in their conflict with microbes, and that they escape into the serum only on the death of the cells. Ruffer, in the researches already referred to, shows that the dead serum of guinea-pigs, which have no immunity, manifests strong toxic action upon the bacilli of quarter-evil, while the living fluids of the same animal have no such power. Hankin's suggestion agrees with the theory of Metchnikoff, and accounts for most, if not for all, of the phenomena on which Buchner and the humoralists lay stress.

In an exhaustive lecture on Immunity, Roux indicates the limited scope of the doctrine of defensive proteids. He points out that they are found in the spleen of a rabbit susceptible to anthrax as well as in that of the more resistant rat; and he thinks it probable that these agents have not their full power till they have been artificially isolated from the organs in which they occur. Guinea-pigs vaccinated against the septicæmic vibrio, or the microbes of blue pus or of hog cholera, are still as susceptible as ever to the corresponding toxines. The microbes and the toxine of tetanus have no effect whatever upon fowls, and yet the blood of fowls cannot destroy the toxine; it acquires this power only when the toxine has been injected into the fowl, and the power varies with the quantity introduced. Time forbids me to follow the whole argument of Roux. He concludes, with Metchnikoff, that acquired immunity consists in the phagocytes becoming accustomed to the products of the microbes, so that the phagocytes attack the invaders more vigorously, and are not repelled by their toxines. Natural immunity, of which less is known, is explained, in many cases at least, by the normal resistance of leucocytes against bacterial poisons. There may be other means for the protection of the organism, but the action of phagocytes is the most common and the most effective. During the present year Metchnikoff has published his researches concerning hog cholera, and these furnish striking confirmation of his main doctrine.

Apart from these abstruse questions, the unknown penetrates deeply into all departments of pathology. In inflammation, great differences of opinion still exist concerning the parts played by leucocytes and by the fixed corpuscles of connective tissue. Ziegler

has recently retracted his teaching concerning the constructive power of leucocytes. He now states, and his view is generally accepted, that they take no share in the formation of new tissue. In catarrhal pneumonia, many authorities hold that the cells which fill the air vesicles are swollen emigrants, not derived from proliferation of epithelium. In tubercle, Sanderson considers it proved that the bacillus has no phlogogenic power, and that it causes tissue proliferation only, while Metchnikoff shows the bacillus provoking abundant diapedesis. Boyce, who agrees with Ziegler's recent teaching, says that "in chronic inflammation, with its marked tissue proliferation and accompanying increased vascularity, one sees the older (Virchow's) view of inflammation. Whilst in well-marked acute inflammation, with its prominent vascular phenomena—notably the leucocytic—and with the less prominent tissue changes, we become acquainted with Cohnheim's view. These extremes merge into one another, on the one hand by the proliferative tissue changes decreasing, and on the other by the vascular phenomena increasing, and *vice versâ.*" It would greatly simplify the task of the teacher if he could point to leucocytes as concerned only in the acute stage of inflammation, and to tissue corpuscles as the sole agents of repair and of productive inflammation. But there is ample room for doubt whether such an absolute differentiation of function is possible.

Concerning dropsy, even in its apparently simple mechanical forms there are factors that elude us. Why in one case does a limited obstruction cause copious effusion, while in another a thrombosis of all the crural veins is unattended with œdema? Of dropsy as a result of heart disease, our knowledge is generally reliable, but it is sometimes at fault. In certain cases of marked valvular incompetence dropsy is absent, while others in which the leakage is relatively slight are attended with abundant œdema. In renal dropsy we distinguish primary acute dropsy of general character with high blood tension from late insidious dropsy affecting the dependent parts and associated with low blood tension. But our knowledge is approximate, not precise. Dickinson has done useful work by insisting on the dynamical factor in the dropsy of both acute and chronic kidney disease; and probably we are on safe ground in referring the late dropsy seen in cases of contracting granular kidney to the progressive dilatation of the

heart; but I am convinced that primary renal dropsy will not be fully understood till the phenomena of the peripheral circulation have been studied much more profoundly, so that we may know how dynamical conditions interact with the chemical constitution of the blood and with the structural and vital changes in the minute vessels.

The origin of tumours is still obscure. Cohnheim's doctrine of persistent embryonic rudiments probably applies to few cases. Sir George Humphry has endeavoured to simplify our ideas by dwelling on the analogy between congenital overgrowths and tumours. The cause of malignancy in tumours is yet to be found. Much has been written about the presence of sporozoa and kindred organisms, but nothing has yet been established. Great interest will attach to the publication of the complete researches of Ruffer and Walker. The classification of malignant tumours according to their origin from the layers of the embryo will possibly not be of long duration. Some test will be found at once more definite and more intimately concerned with the causation of the growth. The relation between these layers, between epithelial cells and the elements of connective tissue, is closer than we are apt to believe. Histology shows us that deep processes of epithelial cells unite with the outrunners of connective tissue corpuscles. In the downgrowths that form in rodent ulcers, these connections sometimes become very manifest, especially when the progress of the growth has caused some traction upon them; the acinous downgrowths may be burst open, but the process is very different from that produced in epithelioma by the active growth of the cells. The origin of the nests in epithelioma requires further study. In many instances the usual description holds good; the marginal cells of the invading columns are flattened in imbricated fashion around the central cells; but, even in this case, two distinct types are found. In one the central cells are hard, horny, wrinkled; in the other they are large, plump, and rapidly proliferating. Thus these central cells may play a passive or an active part in the formation of nests. In some chronic cases, nests originate in an altogether different manner. The invading columns may be seen slowly advancing along the lymph spaces. The lymph current is more or less stagnant. The endothelial cells on the walls of the spaces (or possibly the plasma cells) become swollen, sometimes forming huge plaques. The

epithelial cells gradually surround these swollen elements, and become flattened around them in nest fashion. Vacuolation and inclusion of cells within cells are frequent, and the appearances so produced are strikingly similar to the drawings of so-called sporozoa recently published. These phenomena of epithelial down-growth are beautifully shown in preparations made by my demonstrator, Mr. Cherry.

Instance after instance might be cited to show how limited is our knowledge, how abundant the field open to enquirers. There is room for all tastes and all degrees of capacity. In the department of histology much useful information can be gleaned by any one endowed with patience and the faculty of accurate observation; while the higher problems of pathology furnish full scope for the finest intellect.

It is impossible for me within the limits of this address to do more than touch upon the vast departments of Pharmacology and Therapeutics. How far we have travelled from the mediæval period, with its nauseous mixtures in which all things foul and fair were huddled together! How far even from the pre-Victorian age, with its routine bleedings and purgings, and its complex prescriptions, which were multiple assaults on symptoms rather than remedies for disease. The great aims of the modern practitioner are precision and directness. Take for example a peptonoid tablet, the surface of which is made of pure pepsin to reinforce the gastric ferment, while within, under a coat of keratin, not acted upon in the stomach, is some pure zymin, which will pass with the food into the duodenum and assist in pancreatic digestion. I do not vouch that these objects are attained, but is something to find an attempt to aid the normal processes of digestion stage after stage. The greatest triumphs of pharmacology are undoubtedly found in the antiseptic system of surgery, and in the scientific use of disinfecting agents. But of these it is not now the time nor the place to speak. Let me, however, remind you of a few great advances made in recent years.

Long ago Pasteur proved that he could protect susceptible animals against hydrophobia by subcutaneous injections of a special vaccine. Evidence has steadily accumulated that by this

vaccine the development of hydrophobia can be prevented in persons already inoculated with the virus of rabies. But it was only in the present year that Professor Murri, of Bologna, succeeded in curing a case of actual rabies, in which paralysis was already strongly marked, by the direct introduction of Pasteur's vaccine into the blood.

Concerning tetanus, we have learnt that the disease is due to a bacillus, shaped like a drumstick, which is widely diffused in surface soil, especially when contaminated with organic matter. The cultivation of this bacillus was at first attended with great difficulty, as it seemed absolutely anaerobious. All the early cultures were obtained in an atmosphere of pure hydrogen. But Kitasato found that it could be grown with free access of oxygen, if a percentage of grape sugar were added. In the body, the bacillus is found only at the point of inoculation. The symptoms are due to the toxines elaborated by it, which are formed very slowly, and diffuse very gradually into the system, their formation being aided by the presence of certain other microbes. It is possible to protect rabbits against tetanus by rendering them accustomed to these toxines. The special vaccine consists of a solution of the toxines heated to 140° Fahr., or treated with terchloride of iodine, or with iodine itself. The serum of rabbits so rendered immune contains an antitoxine, which has the power of destroying large quantities of the toxine of tetanus. Guinea-pigs, which are highly susceptible to the disease, may be protected by the introduction of two cubic centimetres of such serum; and Behring and Kitasato finished their invaluable researches by curing guinea-pigs already convulsed with tetanus by the introduction of similar serum. Tizzoni and Cattani, of Padua, have obtained the antitoxine in the solid state by precipitating the serum with alcohol and drying *in vacuo*. Four cases of severe tetanus in man have been cured by hypodermic injections of the antitoxine so prepared. The toxine is apparently converted directly into antitoxine when mixed with the corpuscular juice expressed from the thymus gland.

The tuberculin introduced by Koch has disappointed most of those who have employed it. In regard to surgical tuberculosis, Watson Cheyne concludes that "on the whole, considering the

indefinite length of time that the treatment must be continued, and the danger of leaving it off, it does not come into play in those cases of external tuberculosis which are accessible to other local measures." The greatest success is claimed in tuberculosis of the larynx. Ehrlich's paper published in the *Lancet* puts the general case in favour of tuberculin as strongly as possible. Koch continues sanguine, and has prepared a purer form of tuberculin, free from by-products, with which he hopes to obtain better results. The doses now recommended are very small. It must be borne in mind that the use of tuberculin was based on Koch's assertion that he had by its action arrested the progress of tuberculosis in guinea-pigs. The details of his experiments have not been published. Other observers have failed to obtain any such results. Pfuhl, working in Koch's laboratory, found that small doses of tuberculin, either alone or combined with other treatment, produced no marked effect in inoculated guinea-pigs; but he claims to have been more successful with large doses. In his opinion, local reaction is essential. But all the animals experimented upon by him died of tuberculosis, and the success of the treatment consisted, at most, in a slight mitigation of the disease. Metchnikoff and Roux, in a prolonged series of experiments, found that tuberculin, whether in small or in large doses, is powerless to cure tuberculosis in guinea-pigs. In connection with the use of tuberculin, and all such substances, it is necessary to bear in mind the warning given by Roux—"The injection of products of microbes is not without danger, even when the dosage is restrained. Some, which are well borne at first, cause late troubles, inducing degenerations that may prove fatal." It may be noted that Pfuhl, in his experiments on guinea-pigs, employed mercurials and other agents as adjuvants to the tuberculin injections. Mr. T. N. FitzGerald has a strong belief in the remedial power of mercurials, in small doses, in incipient tubercular affections, especially of joints, and in my opinion these drugs, wisely used, are valuable accessories to other treatment.

Much has been learnt concerning the history of the tubercle bacillus in the body, *teste* the excellent account given by Cornil and Babes in "Les Bactéries"; but possibly much remains to be discovered touching its life outside the body. Mr. Candler, of

Melbourne, has for many years laid stress on the logical necessity for a saprophytic existence of the bacillus external to the living organism. Nocard and Roux, in 1887, showed that the bacilli would grow freely on blood-serum or agar agar, or in broth to which 6–8 per cent. of glycerine had been added. Paulowski succeeded in obtaining cultures on potato. It is now known that in glycerine broth the bacilli will grow, though slowly, at comparatively low temperatures, such as 18°–20° C. Woodhead states that earlier generations so cultivated produce typical tubercles in inoculated animals; but that after several generations have been developed, their virulence may be diminished, although the growths show no loss or even a gain in luxuriance. Hence he remarks that "we have in fact a kind of reversion to the saprophytic condition of the culture, a condition accompanied by diminished parasitic virulence." Cornet's researches concerning the prevalence of the bacillus in the external world obviously need repetition on a much wider basis.

As regards diphtheria, Roux and Yersin have proved that it is due to the Klebs–Loeffler bacillus, that the bacillus is confined to the local lesion, and that all the constitutional symptoms are produced by a soluble poison formed by the bacilli. Reference has already been made to Martin's further researches concerning the nature and action of this poison. A vaccine may be prepared by heating a broth culture of the bacilli for one hour to between 65° and 70° Cent Guinea-pigs inoculated with such attenuated cultures resist the most virulent bacilli when introduced under the skin. As usual in such cases, immunity is not gained at once, about a fortnight being necessary for the mitigated virus to do its work within the system. Attenuated cultures may again be made virulent by growing them along with various micrococci, such as those of erysipelas, or those found in the throat in measles or scarlatina. Roux and Yersin hold that such attenuated microbes are widely distributed in nature and readily regain their toxic power. These researches give us hope that a remedy will soon be found for the most virulent forms of diphtheria. There is encouragement for the larger hope that all the infective diseases, which levy so large a tax on human kind, a tax of death, disease and sore distress, will speedily be brought more and more under subjection. Another illustration is also afforded of the theory of

the origin and disappearance of epidemics enunciated by Pasteur in 1881. Of all the vast additions to our knowledge to which I have referred, how much has sprung from Pasteur's work and Pasteur's influence. *Hommage à Pasteur!* Glory and honour to his name.

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